Update on encephalitis: from infections to autoimmunity

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Disclosures

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Outline

- Update on definition, differential diagnosis, epidemiology
- Update on HSV encephalitis
- Update on VZV encephalitis
- Update on autoimmune encephalitis
- Update on imaging in encephalitis
- Update on management
- Perspectives of ID physicians

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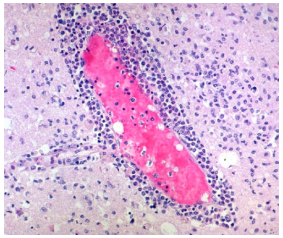
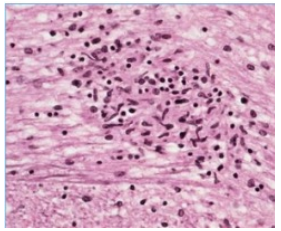
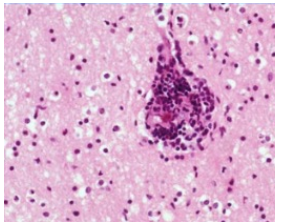
Encephalitis is inflammation of the brain parenchyma

- Pattern of inflammation
  - Diffuse
  - Focal
  - Multi-focal
- May involve other parts of CNS
  - Spinal cord (encephalomyelitis)
  - Meninges (meningoencephalitis)







Clinical criteria

Table 1. Clinical criteria for encephalitis

	IEC criteria for encephalitis[a]
Required	Altered mental status (decreased level of consciousness, lethargy, or personality change) lasting at least 24 h
Additional criteria	Fever at least 38 °C within 72 h before or after presentation Seizures not attributable to preexisting seizure disorder New onset focal neurologic findings CSF WBC count at least 5/mm^3 Brain parenchyma abnormality on neuroimaging suggestive of encephalitis and that is new or acute in onset EEG abnormality consistent with encephalitis and not attributable to other cause

Venkatesan, Curr Opin Inf Dis 2019

Clinical criteria

Table 1. Clinical criteria for encephalitis

	IEC criteria for encephalitis[a]	Graus criteria for autoimmune encephalitis[b]
Required	Altered mental status (decreased level of consciousness, lethargy, or personality change) lasting at least 24 h	Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
Additional criteria	Fever at least 38 °C within 72 h before or after presentation Seizures not attributable to preexisting seizure disorder New onset focal neurologic findings CSF WBC count at least 5/mm^3 Brain parenchyma abnormality on neuroimaging suggestive of encephalitis and that is new or acute in onset EEG abnormality consistent with encephalitis and not attributable to other cause	New focal CNS findings Seizures not explained by a previously known seizure disorder Inflammatory CSF (any two of the following: > 5 WBC/m^3, protein > 45 mg/dl, CSF-specific oligoclonal bands or elevated IgG index) Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Venkatesan, Curr Opin Inf Dis 2019

Infectious causes

- Viruses
  - Sporadic
    - HSV
    - VZV
  - Epidemic
    - Arboviruses
    - Picornaviruses

- Other microbial causes

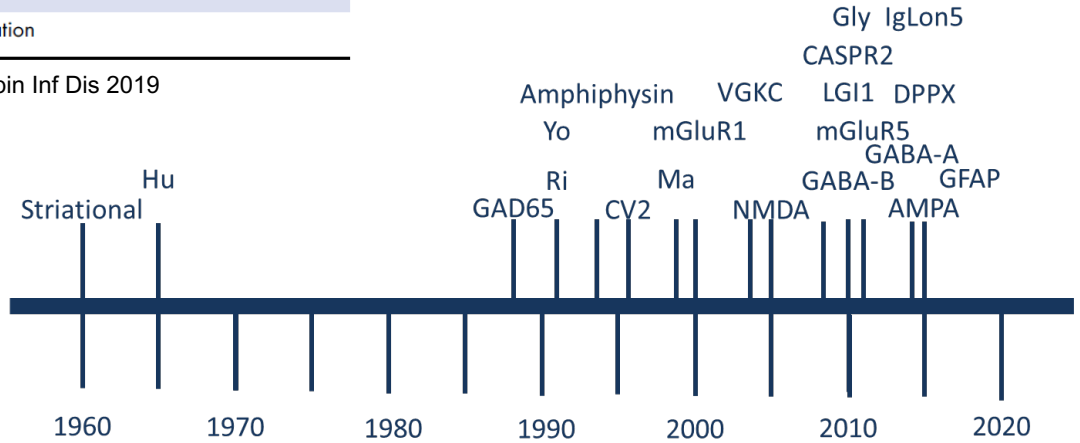
- Togavirus: EEE, VEE, WEE
- Flavivirus: SLE, WN, JV, Dengue, Zika
- Bunyaviruses: LaCrosse, Rift valley fever
- Paramyxoviridae: mumps, measles
- Arenaviruses: LCM, Machupo, etc
- Enteroviruses: Polio, coxsackie, etc
- Reoviruses: CTF
- Rhabdovirus: rabies
- Filoviridae: Ebola, Marburg
- Retroviridae: HIV
- Herpes: HSV1/2,VZV,EBV,CMV,HHV6
- Adenovirus
- Coronaviruses
- Etc...

Autoimmune causes

Table 2. Autoimmune encephalitis

Antineural antibodies
e.g. anti-NMDAR, ant-LGI1, anti-Hu
Hashimoto's encephalopathy (also known as SREAT)
Systemic disease
e.g. SLE, Sjogren's syndrome, sarcoidosis
Demyelinating disease
e.g. ADEM, MOG encephalitis, NMO
Iatrogenic
e.g. CAR-T cell or checkpoint inhibitor-associated encephalitis
Neurodegenerative
e.g. CAA-related inflammation

Venkatesan, Curr Opin Inf Dis 2019



Courtesy of J Probasco

Autoimmune Encephalitis Epidemiology and a Comparison to Infectious Encephalitis

Infectious Encephalitis[a]	No.	Prevalence per 100,000 Population[d]	No.	Incidence per 100,000 Person-Years[d]
All cases	18	11.6	28	1.0
Viral encephalitis				
All cases	13	8.3	18	0.6
HSV1/HSV2	4	2.5	7	0.2
Autoimmune encephalitis				
All cases	21	13.7	24	0.8
Definite autoimmune encephalitis, specific disease with Ab	10	6.5	11	0.4

Dubey et al. Ann Neurol 2018

Approximate worldwide incidence of selected encephalitides

JEV*	10	/1000000/yr
HSV-1	2-4	/1000000/yr
Anti-NMDAR	2	/1000000/yr
TBEV*	2	/1000000/yr
VZV	1	/1000000/yr
Enterovirus	1	/1000000/yr
Anti-LGI1**	1	/1000000/yr
Coxsackievirus	0.25	/1000000/yr

*geographically restricted
** recent estimates suggest a higher incidence

(In U.S., WNV 0.4-1.0/1000000/yr)

Venkatesan et al, Lancet 2019

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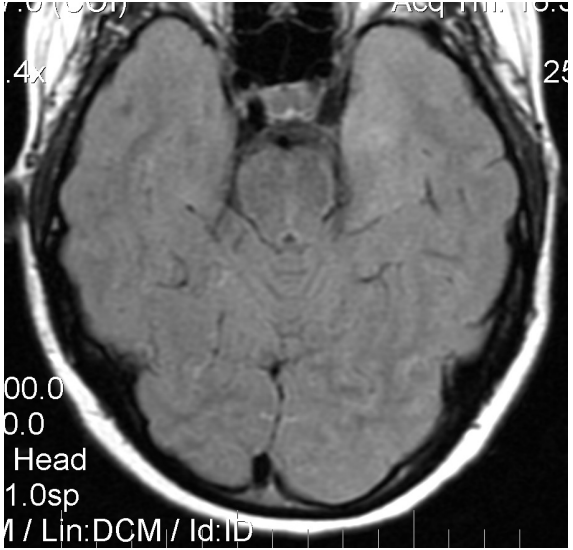
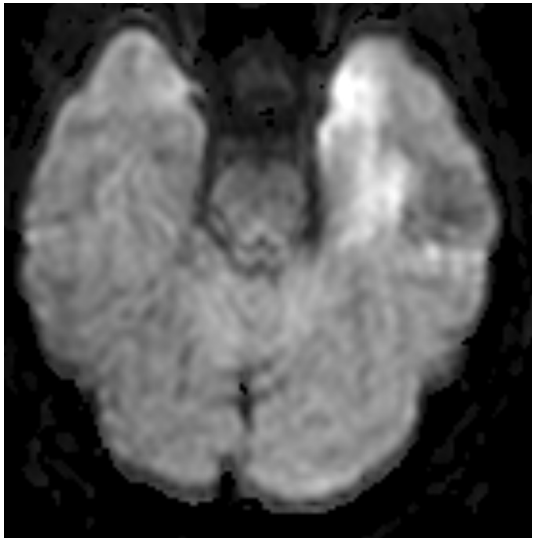
Case

- 60 yo male, no sig PMH
- 5 days of headache, fatigue, intermittent low grade fever, confusion
- Works in chemical plant and describes smelling work scents at home

- In ED: 38.5C
- Na 132, ESR 10; UA and CXR neg
- Head CT unremarkable
- CSF: 180 WBC (95%L), 2 RBC, pro 52 mg/dL (12-60), glu wnl

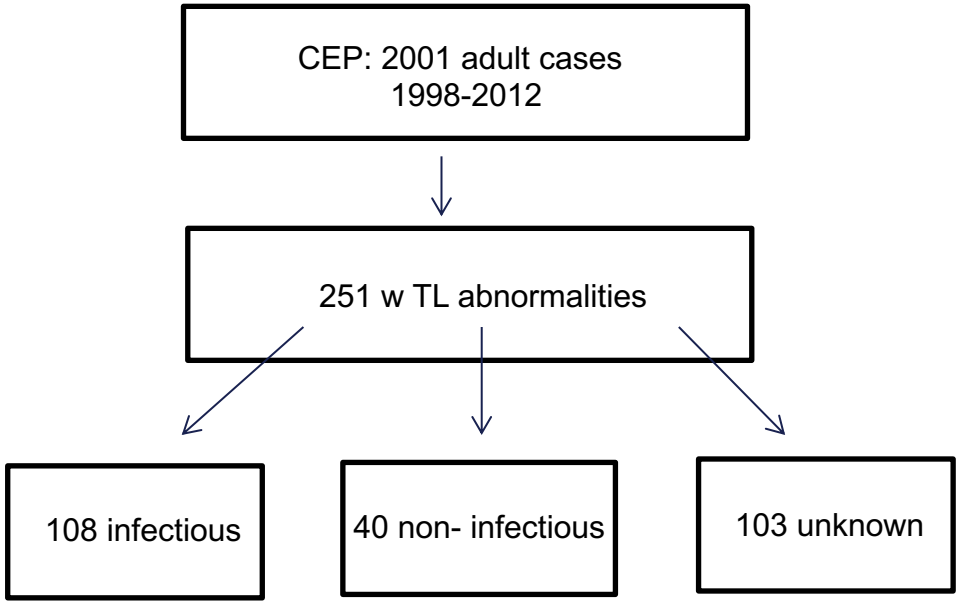
Case





→ CSF PCR + for HSV-1

Use of Clinical and Neuroimaging Characteristics to Distinguish Temporal Lobe Herpes Simplex Encephalitis From Its Mimics



Chow et al., CID 2015

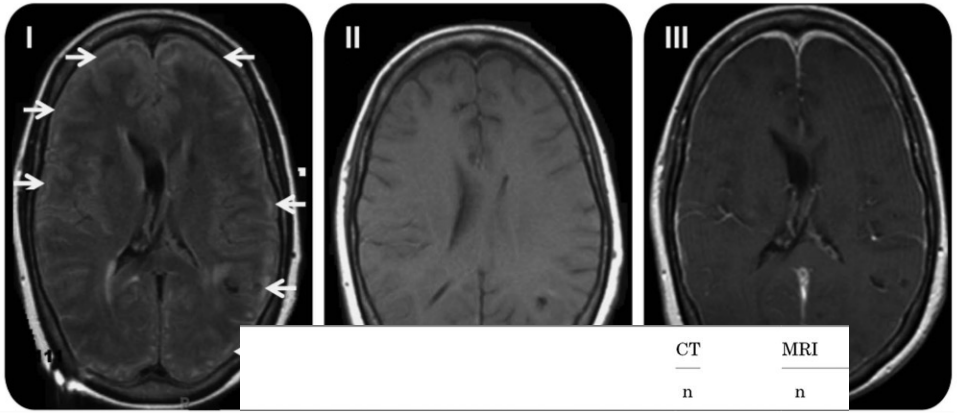
Table 3. Cerebrospinal Fluid and Imaging Characteristics, by Etiology

Characteristic	CSF WBC, Median (IQR)	CSF RBC, Median (IQR)	CSF Protein, Median (IQR)	CSF Glucose, Median (IQR)	
CSF characteristics					
HSE cases (n = 60)	50 (22–76)	48 (12–77)	75 (48–105)	65 (54–74)	
All non-HSE cases (n = 191)	**32 (2–65)[a]**	**33 (2–60)[a]**	**57 (41–96)[a]**	65 (54–82)	
Other non-HSE infectious cases (n = 48)	32 (7–79)	38 (12–66)	66 (47–158)	61 (43–68)	
Autoimmune cases (n = 21)	38 (22–79)	27 (1–74)	54 (33–118)	61 (49–73)	

Characteristic	Bilateral Temporal Lobe, No. (%)	Lesions Outside of Temporal Lobe, Cingulate, or Insula, No. (%)	Restricted Diffusion, No. (%)	Hemorrhage, No. (%)	Enhancement, No. (%)
MRI characteristics					
HSE cases (n = 60)	12/56 (21)	17/56 (30)	16/56 (29)	5/56 (9)	22/56 (39)
All non-HSE cases (n = 191)	**70/153[b] (46)**	**89/158[b] (56)**	34/158 (22)	10/157 (6)	64/159 (40)
Other non-HSE infectious cases (n = 48)	**19/39[c] (49)**	**22/39[c] (56)**	13/39 (33)	**0/39[c] (0)**	19/41 (46)
Autoimmune cases (n = 21)	**10/19[d] (53)**	**12/20[d] (60)**	5/20 (25)	2/20 (10)	10/20 (50)

Chow et al. CID 2015

MRI findings in HSE differ in immunocompromised and in children



Tan et al. Neurology 2012

	CT	MRI
	n	n
Patients who underwent neuroimaging	20	22
Abnormal	14	21
Hemorrhagic component*	4	4
Isolated temporal lobe involvement	6	7
Temporal and other lobe involvement	1	8
Frontal lobe	1	3
Parietal lobe	0	1
Occipital lobe	0	0
Multifocal	0	4
Involvement without temporal lobe	6	5
Frontal lobe	4	2
Parietal lobe	2	0
Occipital lobe	0	0
Multifocal	0	3

*CT and MRI identified 5 different patients with a hemorrhagic component.

To et al. Pediatr Infect Dis J 2014

Pearls: HSE

- CSF PCR may be negative very early in disease course
- MRI DWI is typically the most sensitive sequence
- Hemorrhage is a late finding in HSE and not typically seen
- Immunocompromised or children: atypical presentation and MRI findings
- Acyclovir should be started early!

Relapse of encephalitis following HSE

Up to 20% will experience relapsing neurologic symptoms in the weeks following acyclovir cessation/CSF HSV PCR negative

? Mechanisms: seizures, virologic relapse, immune-mediated relapse

→ Immune-mediated relapse (IgG antibodies to NMDAR or other neuronal antigens)

Adults: median 39 days after onset of HSE (up to 1 year later)
- sx may occur in contiguity with HSE or as a true biphasic presentation
- headache, agitation, confusion
- rare abnormal movements
- CSF normal to low grade WBC pleocytosis
- Brain MRI: increased gadolinium enhancement

Armangue et al. Neurology 2015
Armangue et al. Lancet Neurol 2018

Pearls: HSE

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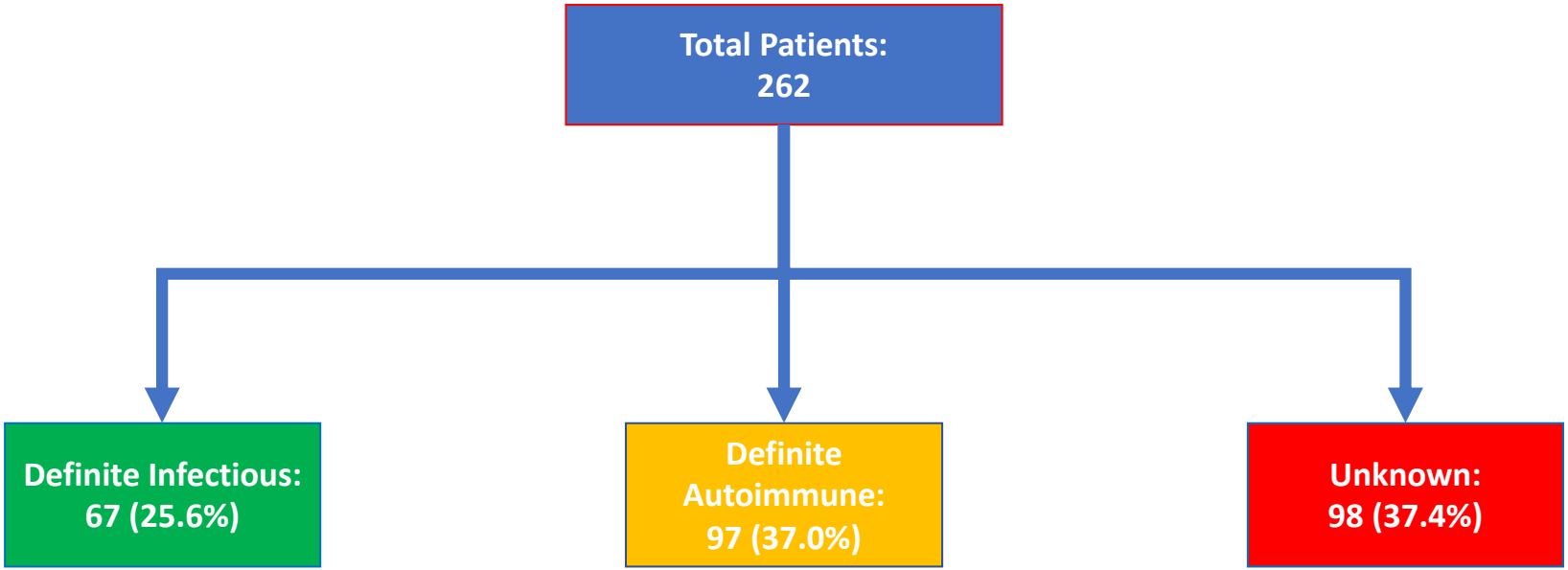
AKI in encephalitis



Zeng et al., unpublished

Bivariate Analyses for AKI after admission:

Variables significantly associated with AKI post admission (p<0.05):

- Race—African American
- Immunosuppression**
- Charlson Comorbidity Index > 1*
- Recent Infection before symptom onset
- Stupor or Coma at presentation*
- FOUR Score < 13
- Hyponatremia (Na <135 mg/dl)*
- Abnormal EEG
- Acyclovir*
- Vancomycin**
- Etiology (autoimmune/infectious encephalitis)*
- Hypotension (< 70 mmHg)
- Thrombocytopenia*
- History of Severe Organ Failure**
- Renal Injury Type (Intrinsic)
- ICU admission
- Mechanical Ventilation*
- In-hospital mortality**

*p-value < 0.01
**p-value < 0.001

Zeng et al., unpublished

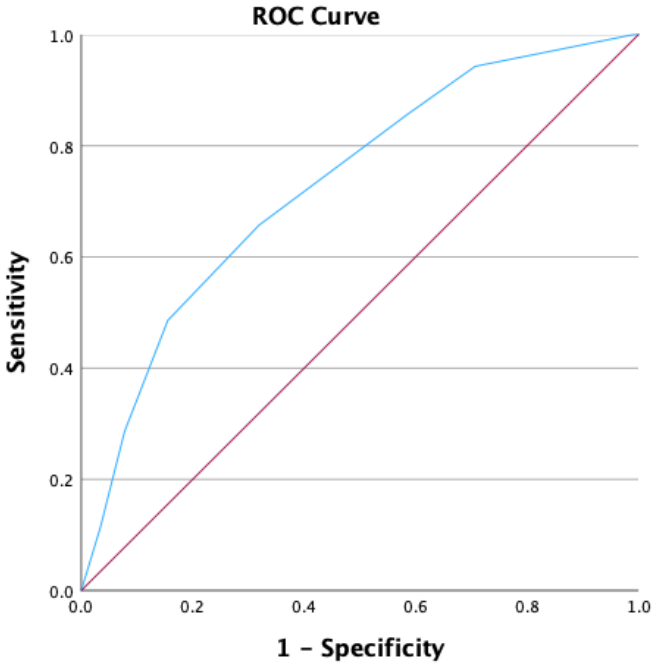
Single-Step Binary Logistic Regression

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	immunosuppression	.490	.511	.921	1	.337	1.633
	Hyponatremia (Na < 135 mg/dl)	.940	.447	4.413	1	.036	2.560
	acyclovir	.183	.572	.103	1	.748	1.201
	vancomycin_use	.586	.497	1.388	1	.239	1.797
	Definite Infectious Encephalitis	.544	.552	.972	1	.324	1.723
	Constant	-2.331	.456	26.091	1	<.001	.097

Zeng et al., unpublished

Single-Step Binary Logistic Regression

- Immunosuppression = 1
- Hyponatremia = 2
- Acyclovir = 1
- Vancomycin = 1
- Infectious Encephalitis = 1



Zeng et al., unpublished

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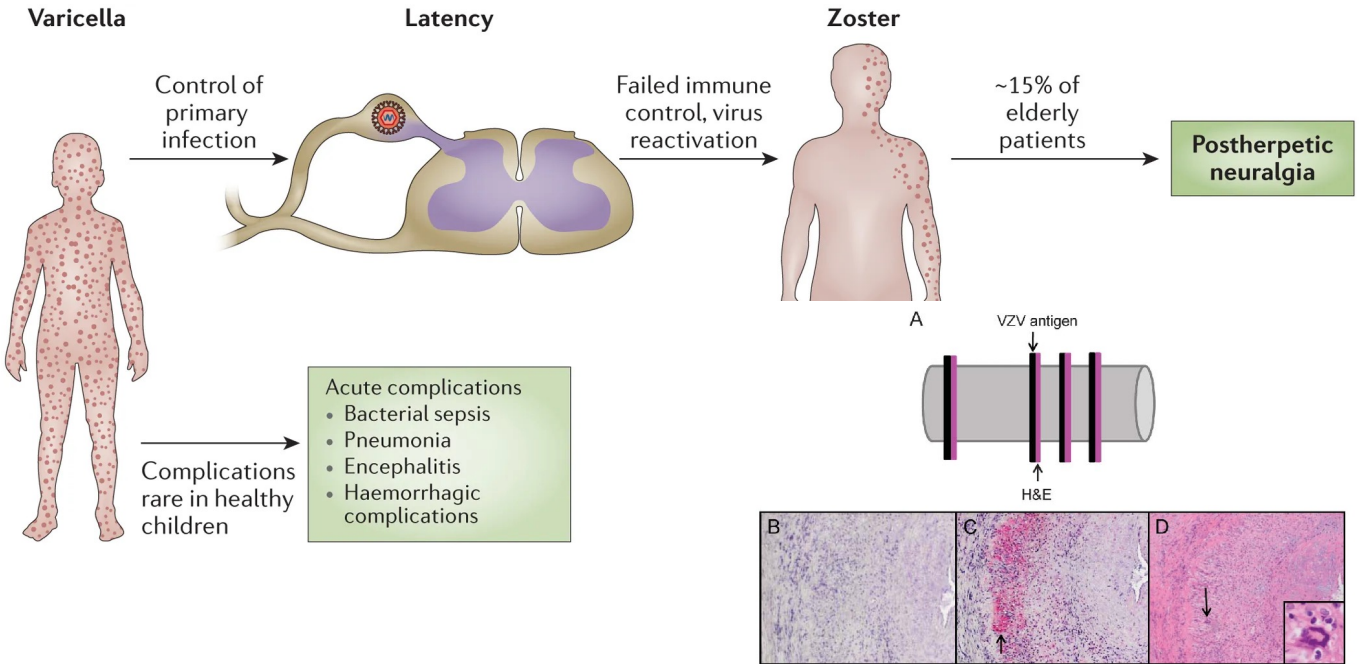
VZV encephalitis

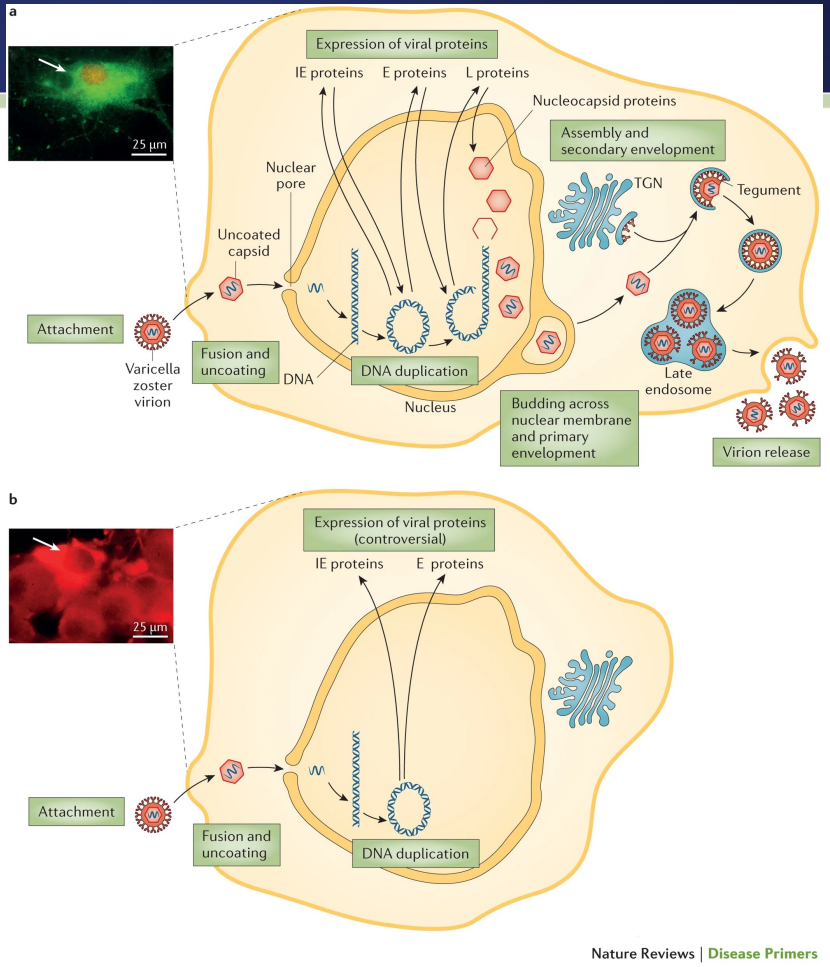
	< 65	65-79	>79	P-value
HSV (%)	27	29	20	0.368
VZV (%)	7	15	30	<0.001
L. monocytogenes	1	7	9	<0.001
TBEV	7	5	0	0.032

Petitgas et al., Infection 2023

VZV latency and reactivation



**Latency/reactivation can occur from both wt and vaccine strains



Lytic

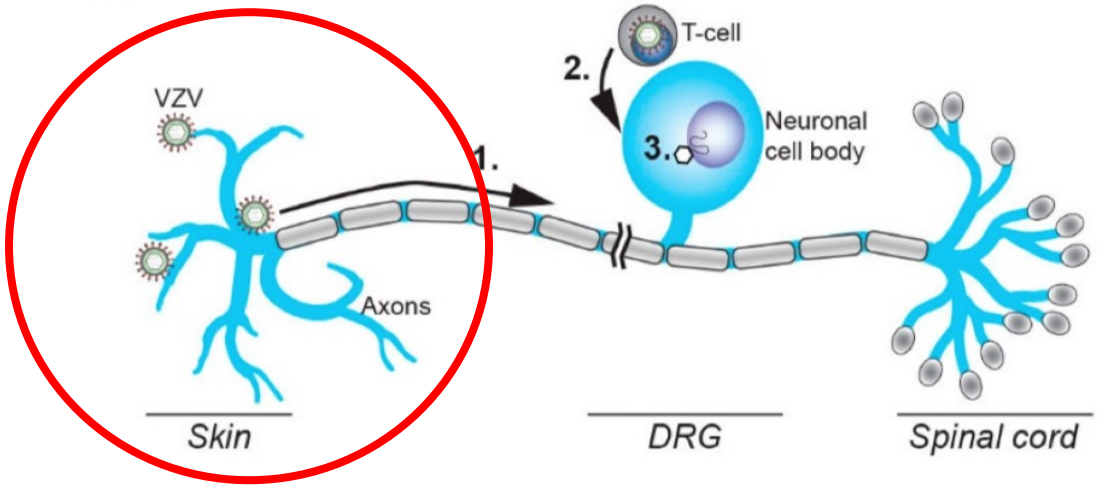
Latent

Pathogenesis of VZV encephalitis

- Exclusively infects humans
  - No robust animal models of disease
- Neuronal infection difficult to model
  - Human fetal neurons
  - Ex vivo experiments with harvested DRGs

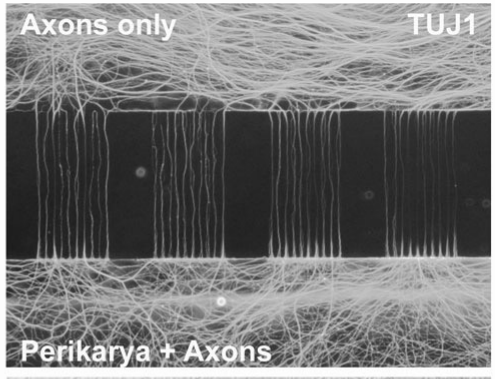
→Use human stem cells to study VZV neuropathogenesis

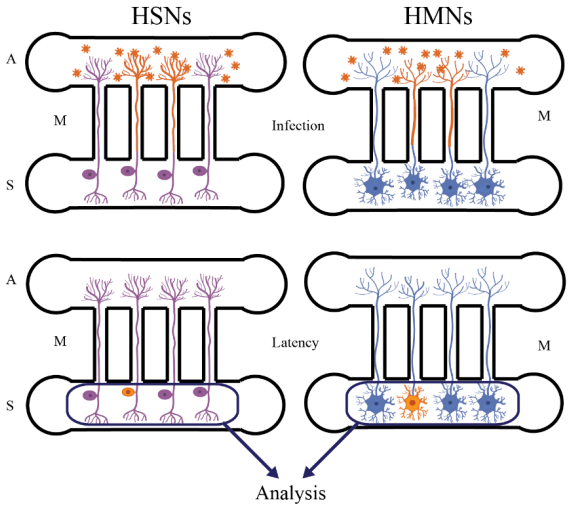
VZV: access to sensory neurons



Depledge et al., Viruses 2018

Axonal infection of HSNs





→ No lytic infection

PCR for
DNA episomal
Configuration?

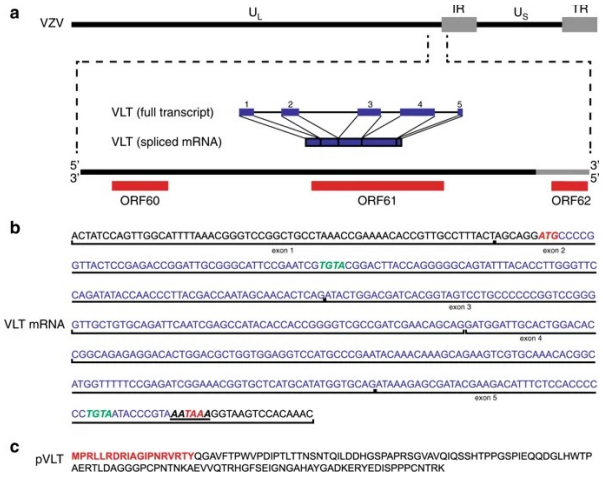
qRT-PCR
viral genes?

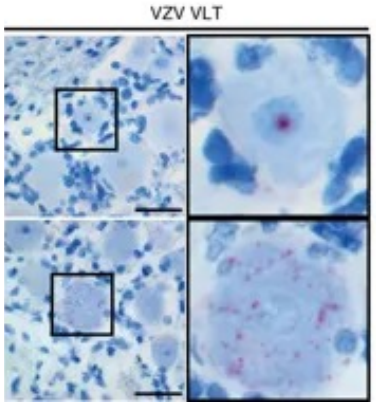
ARTICLE

DOI: 10.1038/s41467-018-03569-2 OPEN

A spliced latency-associated VZV transcript maps antisense to the viral transactivator gene 61

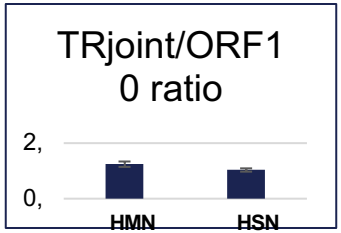
Daniel P. Depledge[1,7], Werner J.D. Ouwendijk[2], Tomohiko Sadaoka[3], Shirley E. Braspenning[2], Yasuko Mori[3], Randall J. Cohrs[4,5], Georges M.G.M. Verjans[2,6] & Judith Breuer[1]

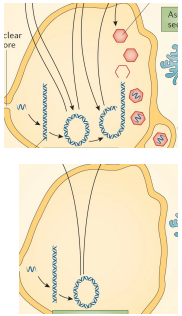


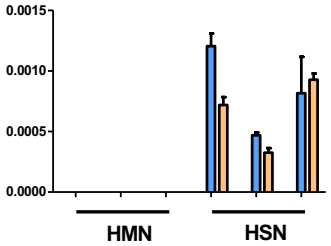


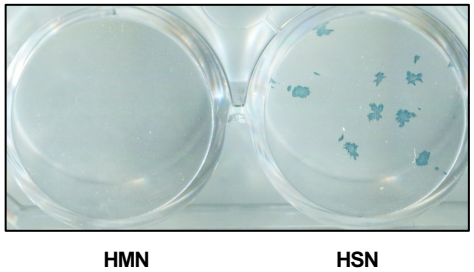
Nature Communications, 2018

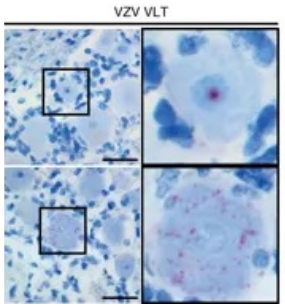
HSNs support VZV latency *in vitro*





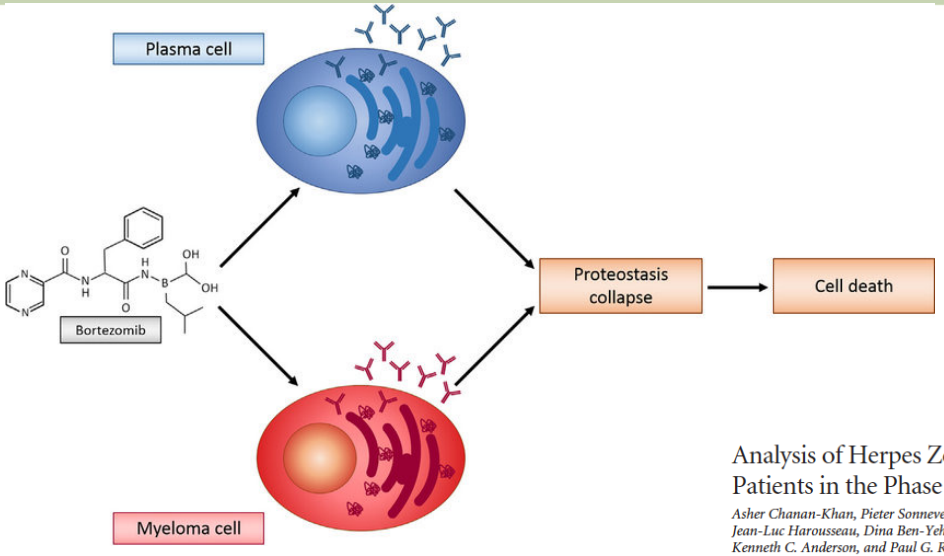






Sadaoka et al., unpublished

Bortezomib and VZV



Analysis of Herpes Zoster Events Among Bortezomib-Treated Patients in the Phase III APEX Study

Asher Chanan-Khan, Pieter Sonneveld, Michael W. Schuster, Edward A. Stadtmauer, Thierry Facon, Jean-Luc Harousseau, Dina Ben-Yehuda, Sagar Lonial, Hartmut Goldschmidt, Donna Reece, Rachel Neuwirth, Kenneth C. Anderson, and Paul G. Richardson

From the Roswell Park Cancer Institute, Buffalo; New York–Presbyterian Hospital, New York, NY; Alta Bates Cancer Center, Berkeley, CA; University of Pennsylvania Cancer Center, Philadelphia, PA; Emory University, Atlanta, GA; Millennium Pharmaceuticals Inc, Cambridge; Dana-Farber Cancer Institute, Boston, MA; University Hospital Rotterdam, Rotterdam, the Netherlands; Hospital Claude Huriez, Lille; Hotel Dieu Hospital, Nantes, France; Hadassah University Hospital, Jerusalem, Israel; Universitaetsklinikum Heidelberg, Heidelberg, Germany; and

A B S T R A C T

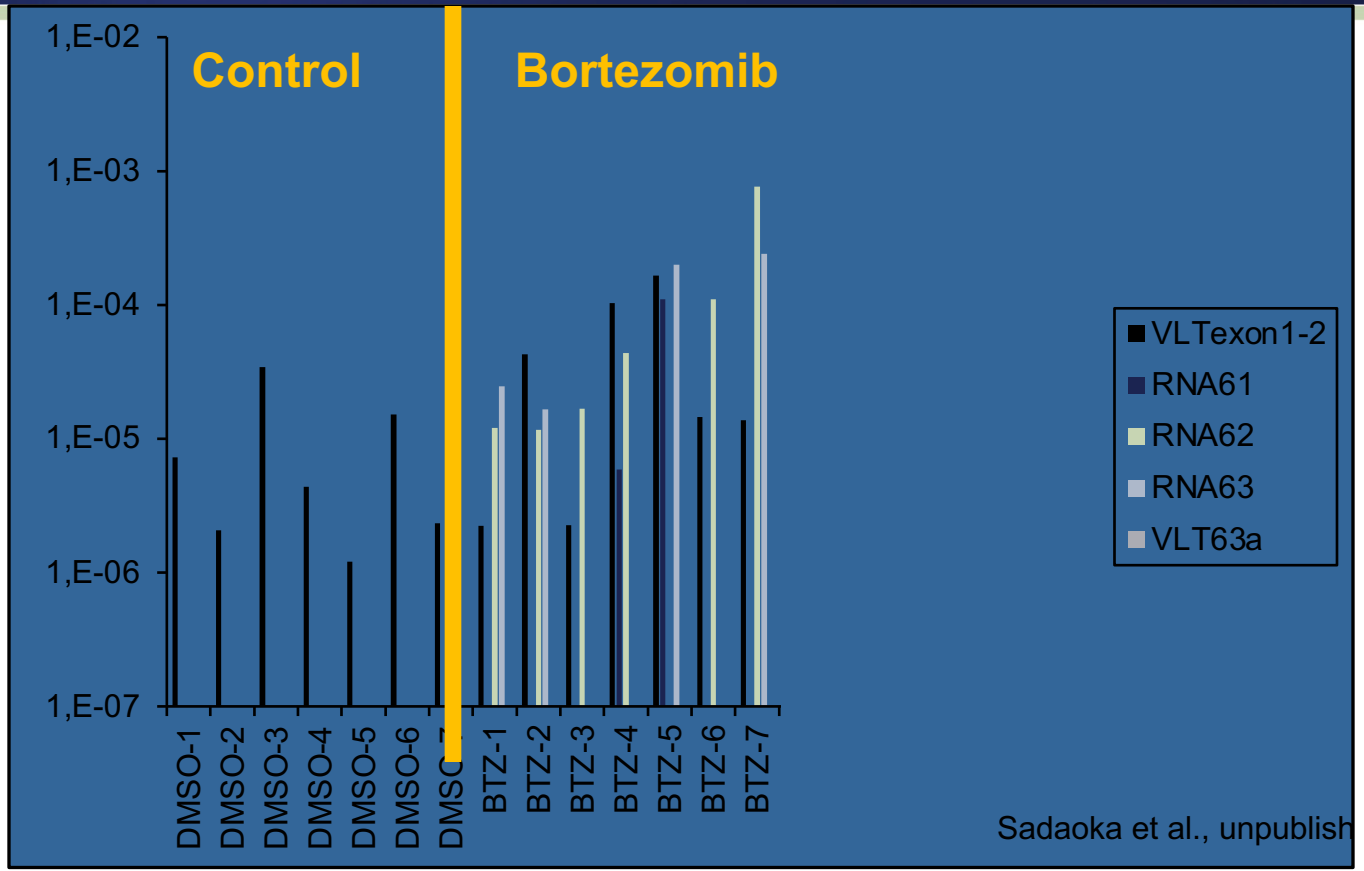
Purpose
The aim of this subset analysis was to determine if bortezomib treatment is associated with increased incidence of varicella-zoster virus (VZV) reactivation in patients with relapsed multiple myeloma (MM).

Patients and Methods
Incidence of herpes zoster was evaluated in 663 patients with relapsed MM from the phase III APEX trial comparing single-agent bortezomib with high-dose dexamethasone.

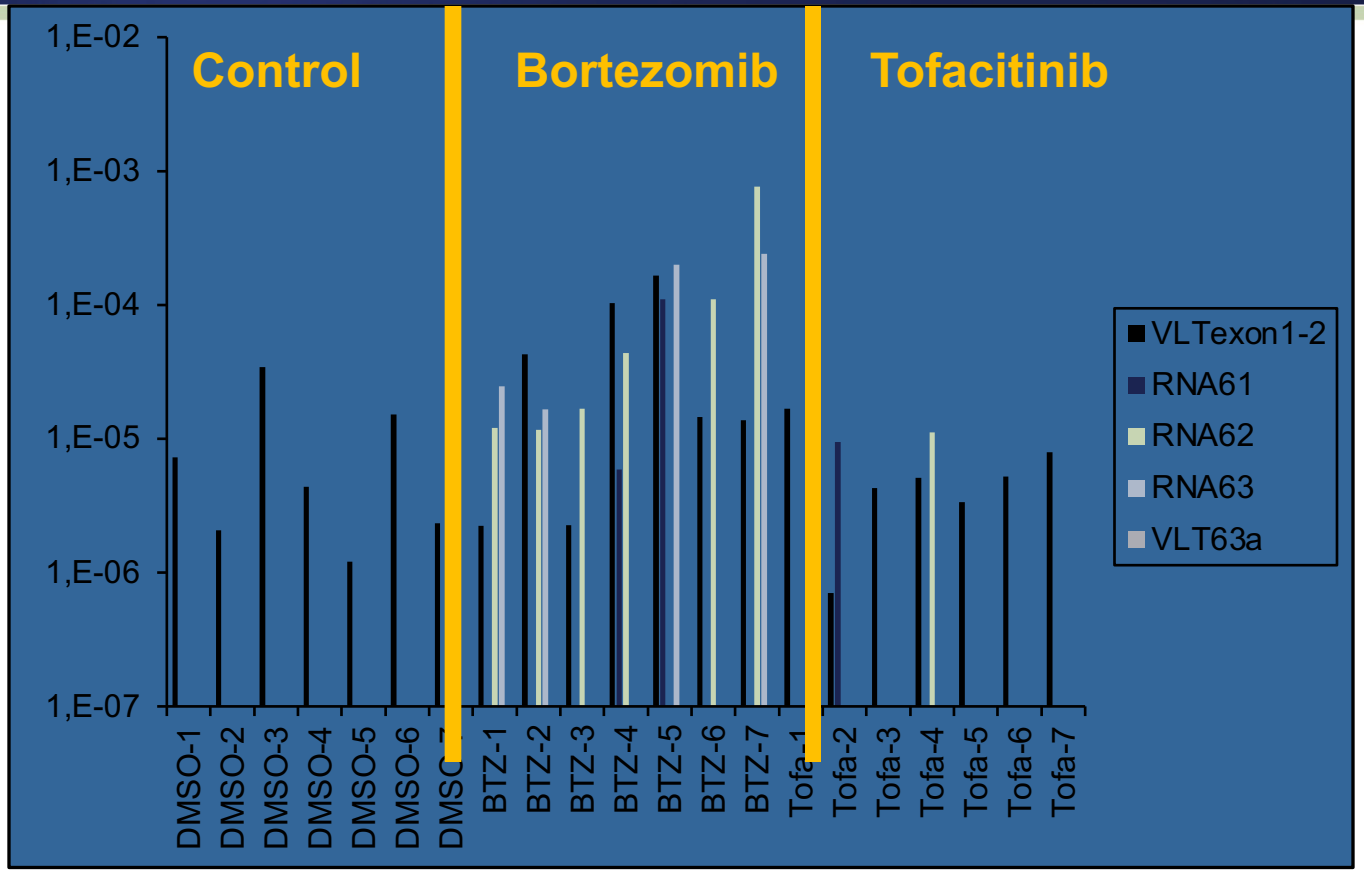
Results
Bortezomib was associated with a significantly higher incidence of herpes zoster compared with dexamethasone treatment (13%, 42 of 331 *v* 5%, 15 of 332; *P* = .0002). Most herpes zoster

Channan-Khan et al., JCO 2008

Bortezomib and VZV latency



Bortezomib and VZV latency



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Case

- 28 yo Indian male
- Software engineer, living in California in a wooded area
- No foreign travel, ill contacts or known animal exposures
  - HA, mild confusion
  - Given Augmentin for “sinus infection”
  - Developed agitation and delusions centered on “Game of Thrones”

Case

- Fever 39 C
- Peripheral WBC 17 (88%N)
- Head CT unremarkable
- CSF pro 45 mg/dL, glu nl, 57 WBC, 89%L

- → Begun on ceftriaxone and acyclovir

- Blood and CSF cultures negative
- CSF viral PCRs (HSV, VZV, enterovirus, WNV) negative

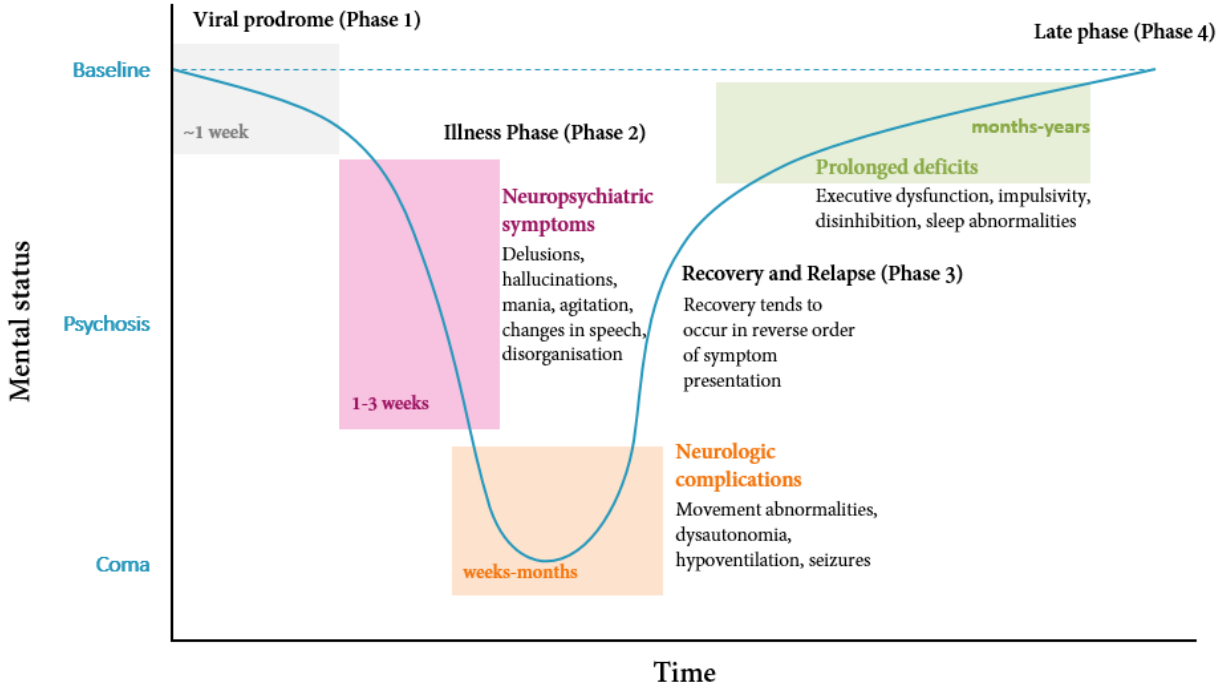
Case

- BP in 200s, HR 160s
- EEG unremarkable
- MRI brain unremarkable

-Repeat LP: 104 WBC, 57%L; pro 86 mg/dL

→ CSF NMDAR antibody positive

PHASES OF ILLNESS IN ANTI-NMDAR ENCEPHALITIS



S Kayser, M., & Dalmau, J. (2011). Anti-NMDA receptor encephalitis in psychiatry. *Current psychiatry reviews, 7*(3), 189-193.

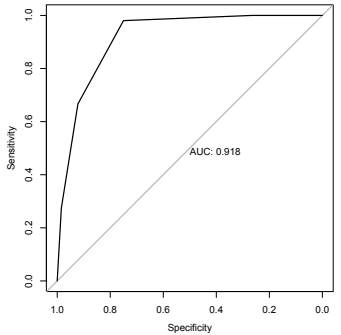
Distinguishing viral from autoimmune encephalitis

Clinical characteristics	Adjusted OR (95% CI)	P value
Age less than 60 years	4.34 (0.56-33.2)	0.157
Charlson Comorbidity Index <2	6.62 (1.05-41.4)	**0.043**
Subacute to chronic (> 6 days) onset	22.36 (2.05-243.7)	**0.011**
Absence of fever	0.23 (0.03-1.44)	0.119
Seizures	7.49 (0.99-56.5)	0.051
Psychiatric and/or memory complaints	203.0 (7.57-5445)	**0.002**
Movement disorders	7.22 (0.85-61.1)	0.069
Absence of robust inflammation in CSF (WBC <50/ul and Protein <50 mg/dl)	0.05 (0.005-0.50)	**0.011**

Granillo et al. , CID (2022)

Distinguishing viral from autoimmune encephalitis

Score result	Viral encephalitis		Autoimmune encephalitis	
Development cohort				
	N =88	%	N =36	%
0	18	20.5	0	0.0
1	33	37.5	0	0.0
2	23	26.1	9	25.0
3	14	15.9	26	72.2
4	0	0.0	1	2.8
Validation cohort				
	N =64	%	N =51	%
0	17	26.6	0	0.0
1	31	48.4	1	2.0
2	11	17.2	16	31.2
3	4	6.3	20	39.2
4	1	1.6	14	27.5



Granillo et al. , CID (in press)

Case

- 31 year old Asian male

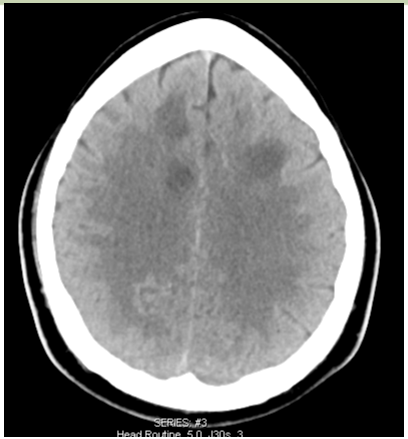
  1 day PTA: Fiancee noted “apathetic”, confused, unable to recognize daughter

  Day of admission: fever, no improvement

Case

- Past history:
  - DM
  - 4 months prior: liver abscess (strep constellatus); tx with PCN X 3 months
  - No sick contacts
  - No IVDU or dental infections
- Admit exam
  - T 101F; tachycardic; hypotensive
  - Awake; oriented only to self
  - Expressive aphasia, psychomotor slowing, abulia
  - Incontinent

Case



- Normal/neg: HIV, Toxo IgM, Trep testing, quantiferon, Whipple PCR
- CSF: 10 WBC (100%L), pro and glu nl

Case

→ Started on vancomycin, ceftriaxone, flagyl for presumed polymicrobial abscesses

→ Mental status worsened

→ Transferred to JHH

Bacterial/fungal/myco cultures negative

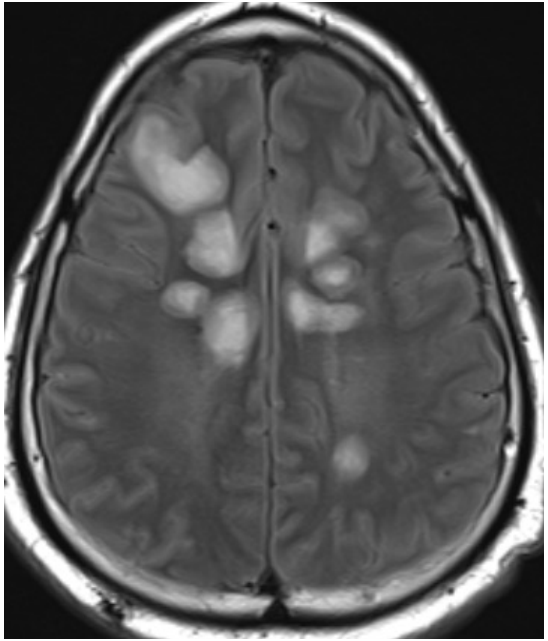
ESR 50

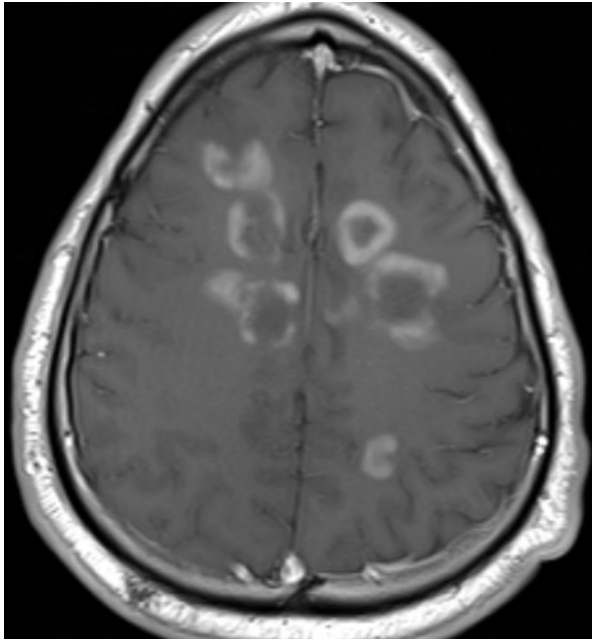
Repeat CSF unchanged

Pan-CT negative (resolution of prior abscess)

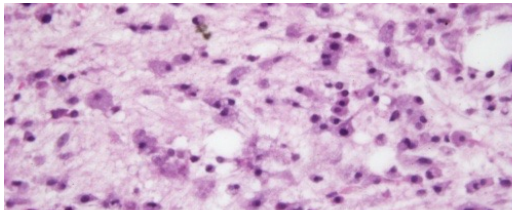
TEE unremarkable

Case

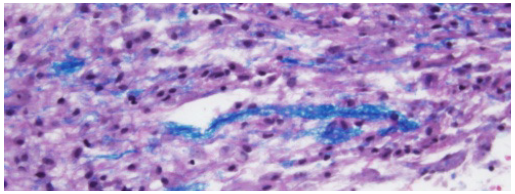




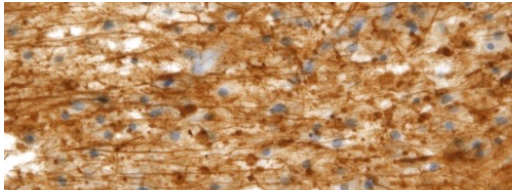
Case: R frontal biopsy



H and E



LFB



NF

Case

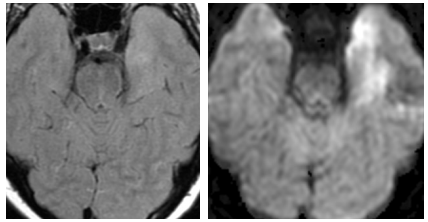
→ Acute disseminated encephalomyelitis (ADEM)

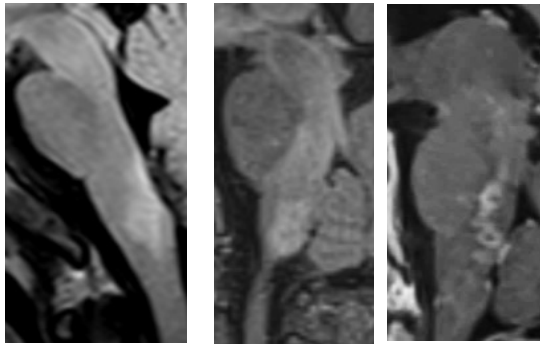
Multifocal inflammatory demyelinating CNS dz
Prodrome→ 1-2 wks → Encephalopathy
Usually monophasic
Postinfectious, postvaccinial, spontaneous

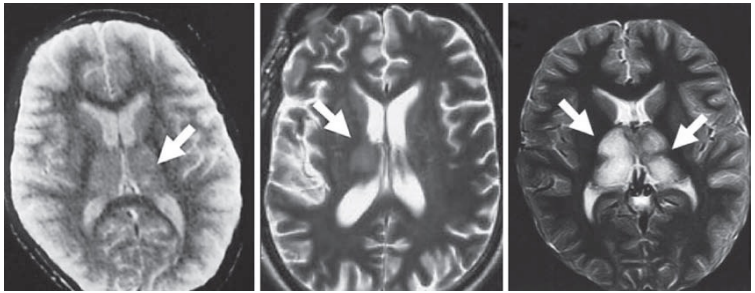
Outline

- Update on definition, differential diagnosis, epidemiology
- Update on HSV encephalitis
- Update on VZV encephalitis
- Update on autoimmune encephalitis
- Update on imaging in encephalitis
- Update on management
- Perspectives of ID physicians

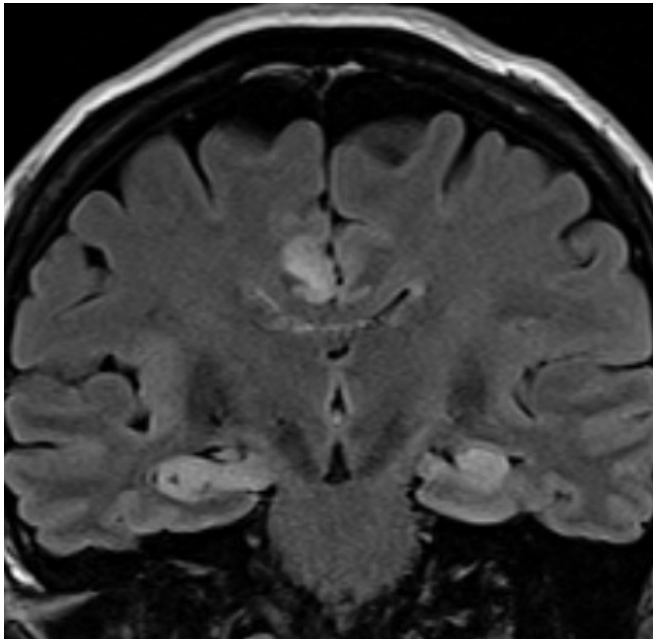
MRI in infectious encephalitis







Autoimmune limbic encephalitis



→ Symmetric mesial temporal lobe involvement

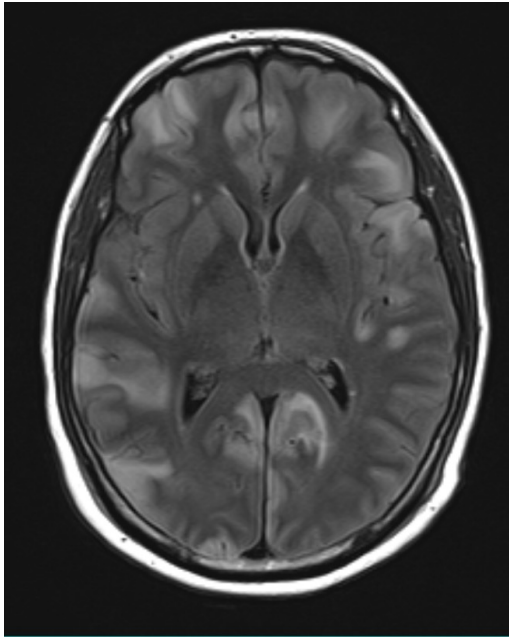
MRI in autoimmune encephalitis

Often abnormal in anti-GABAa receptor encephalitis

Abnormal in 60-70% of ALE

Abnormal in only 30% of anti-NMDAR encephalitis

Normal in most other cases

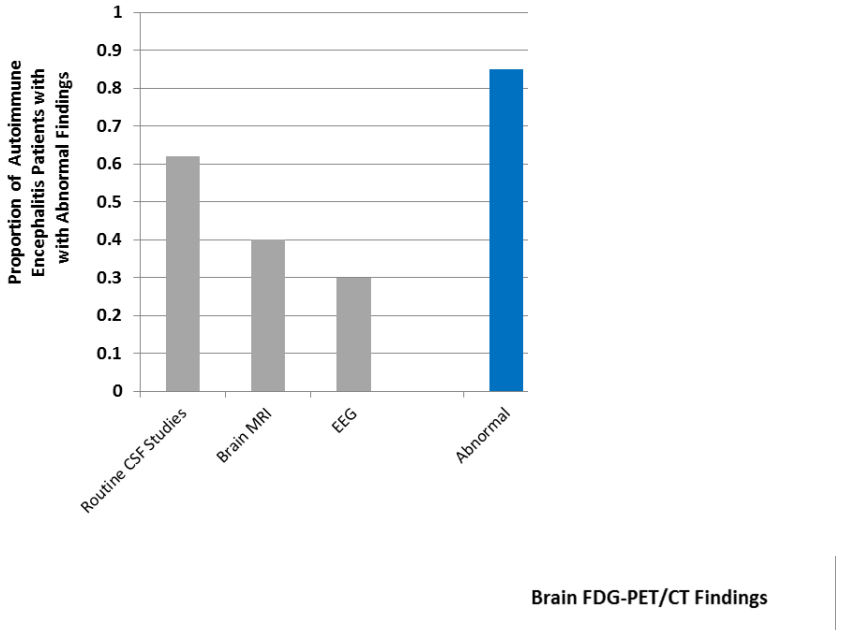


What is the Role of Dedicated Brain FDG-PET/CT in Autoimmune Encephalitis

- **Cases classified per recent clinical diagnostic criteria (Graus et al. Lancet Neurology 2016)**
- Underwent dedicated brain FDG-PET/CT within 3 months of symptoms
- Z-score maps of FDG-PET/CT made using 3D-sterotactic surface projections with comparison to age-group matched control subjects
- **Brain region mean Z-score with magnitude ≥2 interpreted as abnormal**

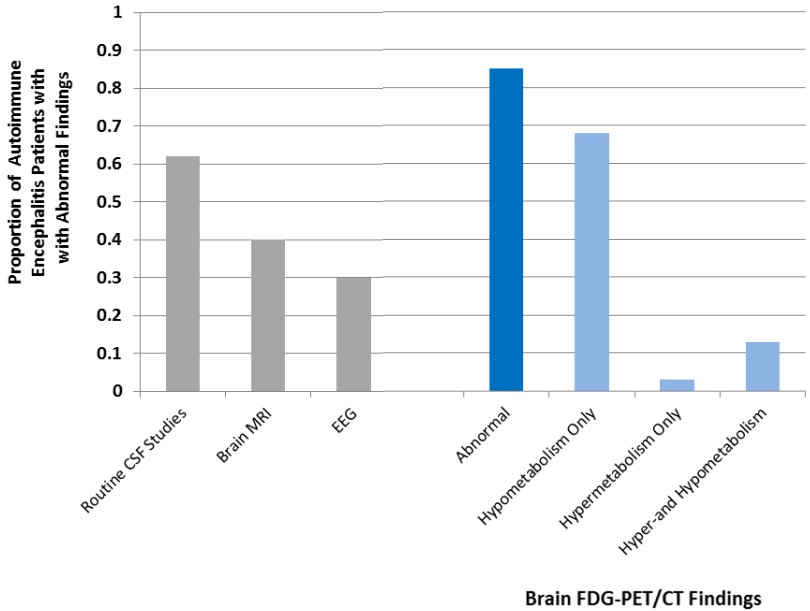
Probasco et al, *Neurology:Neuroimmunol Neuroinflamm* 2017

Brain FDG-PET/CT is Often Abnormal in AE



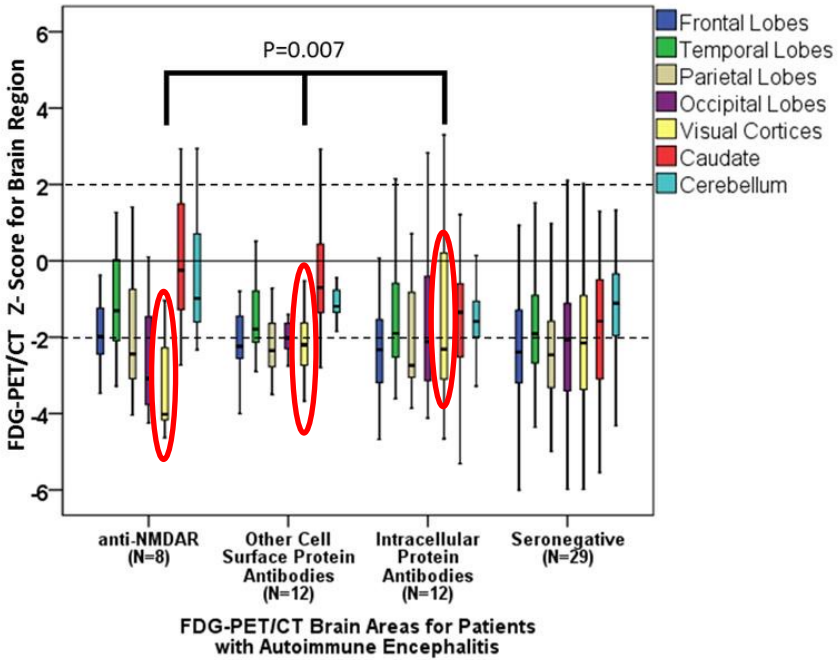
Probasco et al, *Neurology:Neuroimmunol Neuroinflamm* 2017

Brain FDG-PET/CT is Often Abnormal in AE: Hypometabolism predominates



Probasco et al, *Neurology:Neuroimmunol Neuroinflamm* 2017

Occipital Hypometabolism as a Potential Early Biomarker of anti-NMDAR Encephalitis



Probasco et al, *Neurol Neuroimmunol Neuroinflamm* 2018

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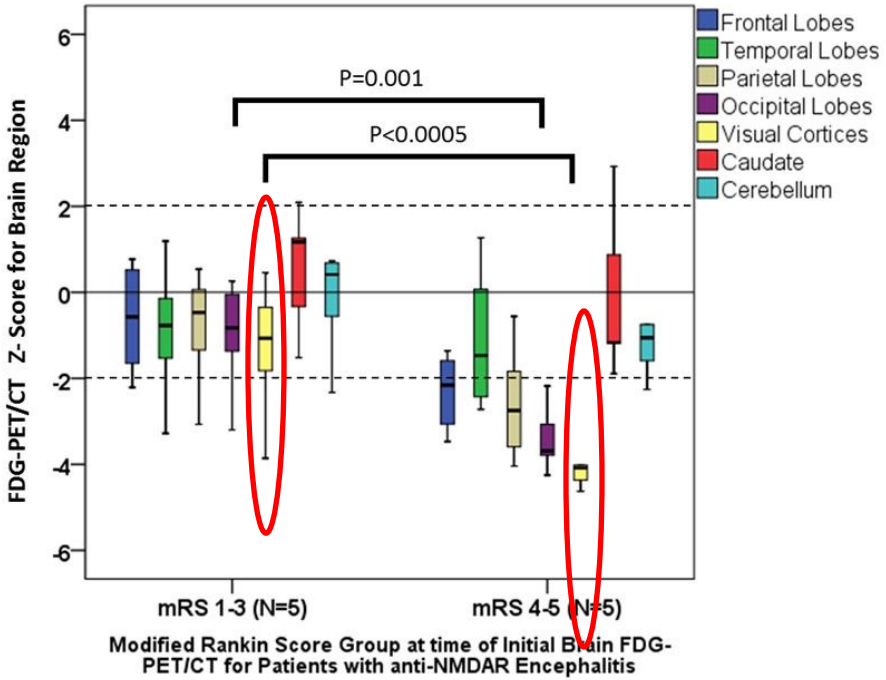

Probasco et al, *Neurology:Neuroimmunol Neuroinflamm* 2018

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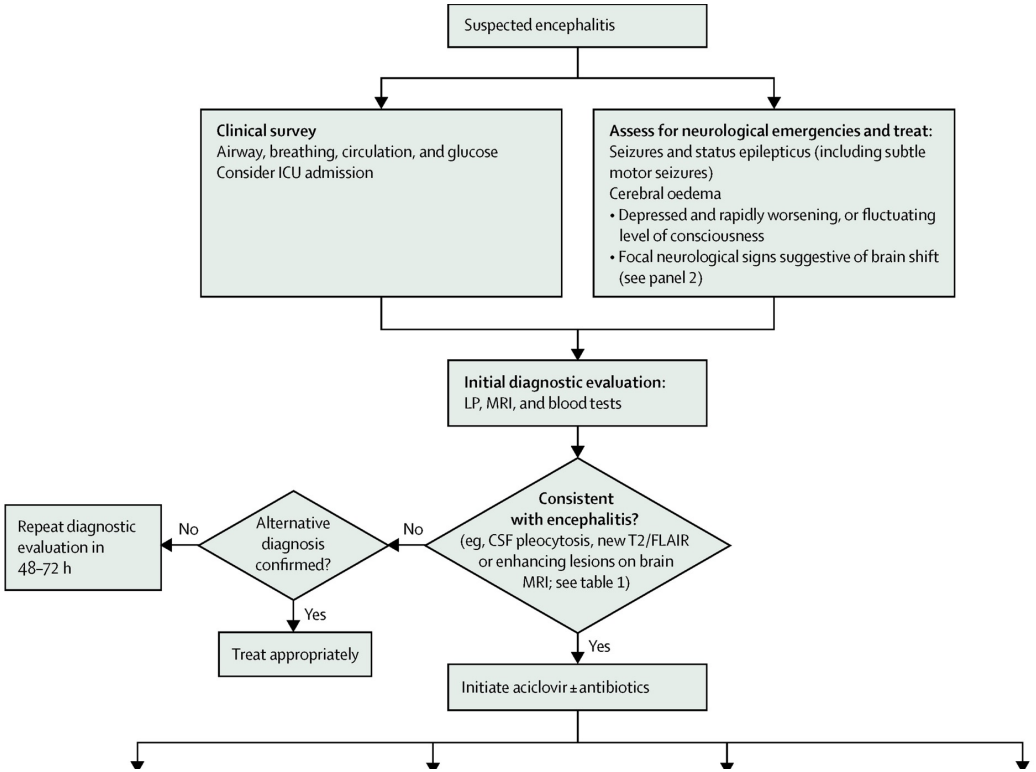
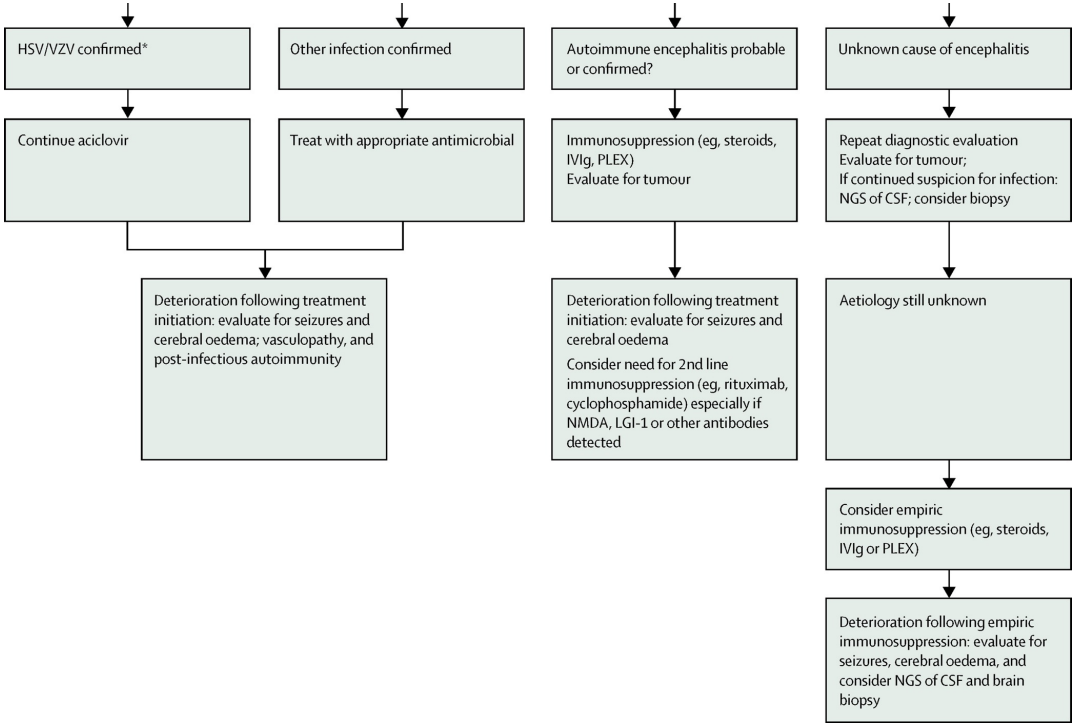
Approach to management



Venkatesan et al., The Lancet 2019

Approach to management



Venkatesan et al., The Lancet 2019

Specific antiviral treatment is limited

CNS infection	Treatment	Comments
HSV encephalitis	Acyclovir 10mg/kg IV q8h for 14-21d	Adequate hydration to avoid renal toxicity from tubular precipitation
VZV encephalitis	Acyclovir 10-15 mg/kg IV q8h for 10-21d (duration poorly defined); valacyclovir 1000mg PO tid suppression may be indicated in immunosuppressed	In cases of vasculopathy or myelitis, short course (5 days) corticosteroids may be of added benefit
CMV encephalitis	Ganciclovir 5 mg/kg IV q12h + foscarnet 90 mg/kg IV q12h for 21d, followed by maintenance	If HIV+, cART should be initiated concurrently
Human herpes virus-6 encephalitis	Ganciclovir 5 mg/kg IV q12h *or* foscarnet 90 mg/kg IV q12h for 21d, followed by maintenance	If toxicity develops to one agent, may change to the other
Herpes B virus encephalitis	Ganciclovir 5 mg/kg IV q12h for 14-21d, followed by valacyclovir 1g PO q8 for 1 yr	Prophylaxis with valacyclovir 1g PO q8 for 14d
EBV encephalitis	Consider corticosteroids, IVIG, or plasmapheresis	Balance with risks, severity of encephalitis
HIV encephalitis	Consider cART initiation with input from experts; regimen may be targeted at CNS penetration in some cases	CNS-IRIS[a] is sometimes treated with corticosteroids
Rabies encephalomyelitis	No effective treatment	Post-exposure prophylaxis with rabies IG and vaccine

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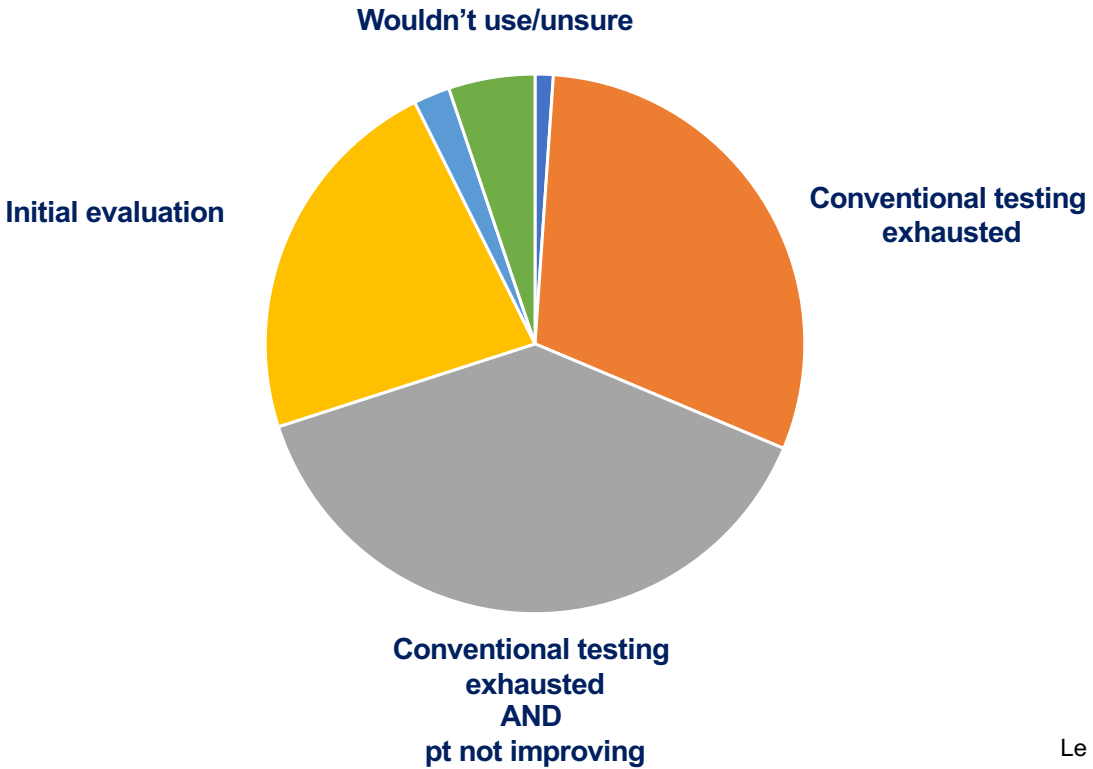
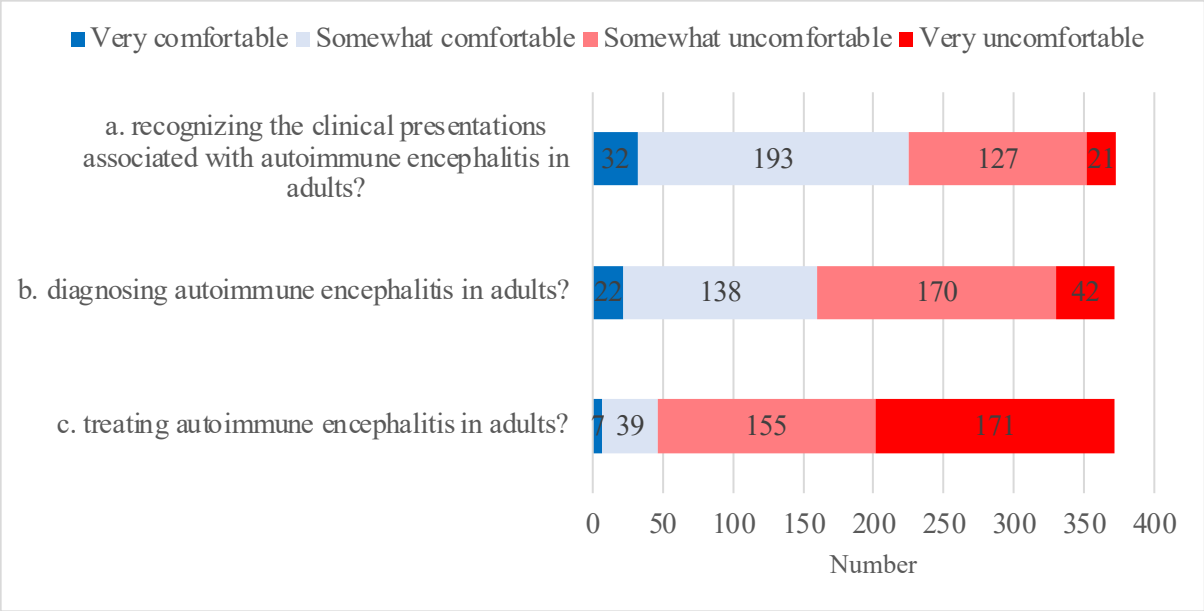
EIN: How would you use NGS in suspected encephalitis?



Le Marechal et al., OFID 2022

EIN: Comfort level with autoimmune encephalitis



Le Marechal et al., OFID 2022

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